Cardiac Function at Rest and During Exercise in Normals and in Patients with Coronary Heart Disease:

Evaluation by Radionuclide Angiocardiography

STEPHEN K. RERYCH, M.D., PETER M. SCHOLZ, M.D., GLENN E. NEWMAN, M.D., DAVID C. SABISTON, JR., M.D., ROBERT H. JONES, M.D.*

From the Department of Surgery, Duke University Medical Center, Durham, North Carolina

This study demonstrates that radionuclide angiocardiography provides a simple and noninvasive approach for evaluation of myocardial function. Previous work concerning myocardial performance has been generally conducted with the patient in the supine position. Radionuclide angiocardiograms were performed in the present study at rest and during exercise in 30 normal subjects and in 30 patients with ischemic coronary artery disease. There were 30 normal controls (Group I), ten with single coronary artery disease (Group II), and 20 patients with multiple vessel coronary disease (Group III). All subjects were studied in the erect posture on a bicycle ergometer. In the *normal* controls, the mean heart rate doubled and the cardiac output tripled during exercise. Intensive training can lead to extraordinary levels of cardiac performance as shown in a world-class athlete who during peak exercise attained a heart rate of 210, an ejection fraction of 97%, and a cardiac output of 56 liters per minute. In the patients with coronary artery disease, both groups were able to increase cardiac output to approximately twice the resting value. The magnitude of increase in blood pressure during exercise was not significantly different in the three groups. However, definite changes were present in the end-diastolic volume at rest compared with exercise. The mean end-diastolic volume at rest was 116 and rose to 128 ml in Group I, 93 rising to 132 ml in Group II, and 138 increasing to 216 ml in Group III. The stroke volume increased comparably in all three groups, but the ejection fraction from rest to exercise showed a marked contrast in the controls compared to those with multivessel coronary disease. The ejection fraction rose in Group I from 66 to 80% during exercise, while in Group II it fell from 69 to 67%, and in Group III from 60 to 46%. These findings indicate that patients with ischemic myocardial disease respond to the stress of exercise by cardiac dilatation to maintain or increase stroke volume at increased heart rates. Moreover, the magnitude of this response appears to be greatest in patients with left main coronary artery stenosis. This approach for evaluating myocardial function during exercise provides useful data of importance in selecting medical versus surgical management of patients with ischemic coronary artery disease.

Presented at the Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 5–7, 1977.

* Investigator, Howard Hughes Medical Institute.

Supported by NIH Grant No. 5 R01 HL 09315-14.

THE RECENT DEVELOPMENT of radionuclide angiocardiography provides a simple approach useful for evaluating patients during submaximal and maximal exercise.[4,16,24,31,34] The purpose of this study is to document the hemodynamic response in normal erect subjects and patients with myocardial ischemia due to coronary artery disease during maximal and submaximal exercise on the bicycle ergometer.

Radionuclides which distribute in the myocardium proportional to coronary blood flow have been used in exercising patients to evaluate regional perfusion disturbances.[22,25,35] Experimental observations have suggested that regional abnormalities of left ventricular function may reflect myocardial ischemia.[26] The present study was designed to evaluate cardiac performance by the first transit of a radionuclide bolus through the central circulation to measure the cardiac output, pulmonary transit time, pulmonary blood volume, left ventricular end-diastolic volume, and ejection fraction throughout the cardiac cycle. Exercise in the erect position was selected because of the similarity to daily activities which commonly impose exercise stress upon patients. The radionuclide procedure used in this study provides measurements during rest and exercise with accuracy and simplicity and is quite practical for routine clinical use.

Methods

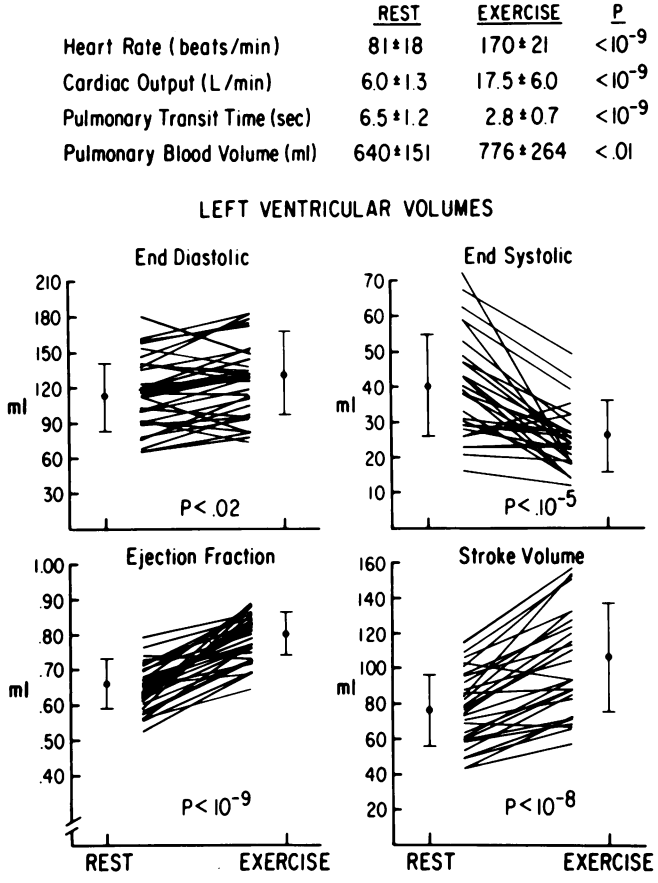
Study Groups

Radionuclide angiocardiograms were obtained in 60 subjects who were admitted to Duke University

0003-4932-78-0500-0449-0125

TABLE 1. *Hemodynamic Values in 30*

Subjects	Sex	Age (yrs)	BSA (m^2)	Heart Rate (beats/min)		Mean Blood Pressure (mm/Hg)		C.O. (L/min)		C.I. (L/min/m^2)		E.F.		EDV (ml)	
				Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
1. D.P.	M	27	1.96	90	140	86	93	6.9	9.4	3.5	4.8	.62	.83	112	81
2. J.S.	M	27	2.15	65	168	76	113	6.3	20.9	2.9	9.7	.72	.82	135	152
3. N.P.	F	27	1.48	86	180	97	113	5.1	13.0	3.4	8.8	.68	.77	88	94
4. S.K.	F	29	1.36	80	170	67	118	4.7	11.8	3.5	8.6	.64	.83	92	83
5. J.M.	F	30	1.72	82	173	88	110	4.4	14.8	2.6	8.6	.64	.76	85	112
6. P.L.	M	34	2.07	100	180	94	101	7.9	21.5	3.8	10.4	.66	.83	119	144
7. J.A.	M	36	1.90	60	164	93	140	4.7	18.0	2.5	9.5	.79	.85	99	129
8. A.S.	M	43	1.94	65	160	113	119	5.6	16.9	3.4	8.7	.70	.80	117	132
9. L.J.	F	48	1.81	90	158	89	127	4.0	11.5	2.2	6.4	.66	.76	67	96
10. D.J.	M	48	1.74	85	175	107	100	5.5	15.3	3.1	8.8	.52	.69	123	126
11. G.K.	M	25	1.90	80	180	86	120	6.0	20.8	3.2	11.0	.67	.88	113	131
12. D.H.	F	53	1.76	115	156	130	137	5.8	10.2	3.3	5.8	.76	.84	66	78
13. H.R.	M	60	2.20	86	162	92	109	6.5	18.0	3.0	8.2	.63	.85	144	131
14. G.H.	F	31	1.76	120	150	93	103	6.4	14.1	3.6	8.0	.63	.80	100	118
15. P.S.	M	33	1.91	80	180	96	109	6.7	25.2	3.4	13.2	.56	.77	146	178
16. G.P.	F	29	1.72	72	188	98	109	3.6	13.5	2.1	7.9	.66	.69	76	104
17. J.F.	M	45	2.01	118	150	52	105	5.0	8.7	2.5	4.3	.65	.71	65	81
18. J.H.	M	24	2.00	65	210	82	110	6.9	27.8	3.4	13.9	.59	.88	180	150
19. B.B.	M	23	1.91	58	190	91	134	6.7	29.8	3.5	15.6	.71	.86	162	183
20. D.R.	M	25	1.96	68	195	100	100	6.3	24.9	3.2	12.7	.76	.83	121	154
21. A.S.	M	23	1.84	69	200	74	103	6.5	23.0	3.5	12.5	.69	.86	139	134
22. M.C.	M	23	1.90	70	190	117	127	7.6	28.7	4.0	15.1	.69	.86	158	175
23. C.R.	F	24	1.54	70	165	91	107	4.2	14.5	2.7	9.4	.67	.79	90	111
24. C.H.	M	24	1.90	73	150	92	122	6.1	23.0	3.2	12.1	.61	.84	137	183
25. J.C.	M	55	2.22	50	120	82	90	5.0	18.4	2.3	8.3	.63	.89	160	172
26. V.P.	M	29	1.92	95	210	99	123	7.0	19.8	3.7	10.3	.74	.73	100	129
27. B.B.	M	38	1.94	90	156	83	133	9.2	14.6	4.7	7.5	.73	.75	140	125
28. S.L.	M	25	1.78	70	160	82	105	4.2	10.9	2.4	6.1	.58	.72	103	95
29. C.P.	F	31	1.74	102	152	94	107	7.1	12.6	4.1	7.3	.60	.72	116	115
30. J.K.	F	36	1.45	90	156	81	95	7.7	13.7	5.3	9.4	.56	.64	153	137



Medical Center over a period from September 1976 to August 1977. There were 30 normal controls (Group I). In addition 30 patients were evaluated for chest pain, in whom a diagnosis of coronary artery disease was established. Ten of these patients had significant *single vessel* coronary artery disease (Group II), and 20 had *multi-vessel* coronary involvement (Group III).

The mean age of the controls in Group I was 34 years with a range of 23–60 years. Twenty subjects were male and ten were female with a mean body surface area of 1.85 $m.^2$ None of these controls had a history of chest pain, hypertension, myocardial infarction, or documented infarction on electrocardiogram. The history and physical examination in each were negative for other diseases related to the cardiopulmonary system.

Each patient within Groups II and III had a baseline evaluation consisting of electrocardiogram, chest film, and coronary arteriography, as well as hematologic and chemical blood profiles. In addition, Bruce stress treadmill testing was performed prior to cardiac catheterization.[5] Resting and exercise radionuclide studies were performed either one or two days prior

FIG. 1. Effects of exercise on left ventricular function in normal erect subjects. Mean age 34 years. (⧳ represents mean values and standard deviation of the mean from rest to exercise).

Normal Subjects at Rest and Exercise

EDV (ml/m²)		SV (ml)		SV (ml/m²)		ESV (ml)		ESV (ml/m²)		PTT (sec)		PBV (ml)		PBV (ml/m²)	
Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
57	41	69	67	35	34	43	14	22	7	5.4	3.0	621	470	317	240
63	71	97	124	45	58	38	27	18	13	7.5	2.7	789	940	367	437
59	64	60	72	41	49	28	22	19	15	4.4	2.4	374	520	253	351
68	61	59	69	43	51	33	14	24	10	4.9	2.1	386	411	284	302
49	65	54	85	31	49	31	27	18	16	5.5	2.4	403	590	235	343
57	70	79	120	38	58	40	24	19	12	6.2	3.1	816	860	394	415
56	68	78	110	41	58	21	19	11	10	7.8	2.4	607	719	320	378
60	68	88	105	45	54	29	27	15	14	7.0	2.1	655	591	338	304
37	53	44	73	24	40	23	23	13	13	6.9	2.8	456	537	252	297
71	72	64	87	37	50	59	39	34	22	7.7	4.2	700	1068	402	613
59	69	75	116	39	61	38	15	20	8	6.5	2.0	654	694	344	365
38	44	50	66	28	38	16	12	9	7	5.4	3.2	522	544	297	309
52	60	76	111	35	50	38	20	17	9	7.4	2.8	802	840	364	382
57	67	61	94	35	53	39	24	22	14	5.5	2.7	584	635	332	361
76	93	82	133	43	70	64	45	34	24	5.9	2.3	645	966	338	506
44	60	50	72	29	42	26	32	15	19	—	—	—	—	—	—
32	40	42	58	21	29	23	24	11	12	6.5	3.7	542	535	269	266
90	75	106	132	53	66	74	18	37	9	6.8	1.3	782	602	391	301
85	96	115	157	60	82	47	25	25	13	6.7	3.0	748	1490	392	780
62	79	92	128	47	65	29	26	15	13	6.5	2.5	679	1038	347	529
76	73	96	115	52	63	43	19	23	10	6.5	3.1	704	1188	383	646
83	92	109	151	57	79	49	25	26	13	7.1	2.1	902	1004	475	528
58	72	60	88	39	57	30	23	19	15	6.0	2.8	420	677	273	439
72	96	84	154	44	81	53	29	28	15	7.4	2.5	753	960	396	505
72	77	101	153	46	69	59	19	27	9	9.6	4.0	806	1225	363	552
52	67	74	94	39	49	26	35	14	18	5.3	1.8	622	594	324	309
72	64	102	94	53	48	38	31	20	16	4.8	2.6	736	633	379	326
58	53	60	68	34	38	43	27	24	15	6.0	3.0	420	537	236	307
67	66	70	83	40	48	47	32	27	18	5.6	4.6	665	967	382	556
106	94	86	88	59	61	67	49	46	34	6.8	2.9	875	662	603	456

to the catheterization-angiocardiographic study or one to two days prior to elective surgical saphenous vein bypass grafting in those who had arteriograms previously. Propranolol was discontinued 36–48 hours prior to radionuclide studies and nitroglycerin was not administered for a period of eight hours prior to testing. No patient with coronary artery disease had a recent myocardial infarction, but 13 patients had prior myocardial infarction documented by a 12-lead resting electrocardiogram, vectorcardiogram, or positive muscle band CPK isoenzymes. Cardiac catheterization consisted of standard left ventriculography for determination of wall motion abnormalities, ejection fraction, volume and pressure data in addition to coronary arteriography. Each of the ten patients in Group II with "significant" one vessel coronary artery disease had a 75% or greater stenosis of a major coronary artery demonstrated by arteriography. The mean age in this group was 47 years (range 34–69). Five patients were male and five were female with a mean body surface area of 1.76 m². The 20 patients in Group III had significant lesions of more than one major coronary artery, including five patients with significant left main stenosis (>75%). The mean age of this group was 53 years (range 38–67). Nineteen patients in Group III were male and one female with an average group body surface area of 1.93 m². In the two groups with documented coronary artery disease, none had evidence of valvar heart disease. In those patients with documented myocardial infarction, exercise radionuclide testing was performed at least three to four months after infarction.

Studies were performed in the erect sitting position during rest and exercise on a Tunturi bicycle ergometer.® After informed consent was obtained from each subject, baseline supine measurements of blood pressure using a standard sphygmomanometer and heart rate as recorded from the modified limb lead CM-5 were recorded. Local anesthesia was used over the skin area of either the external jugular or antecubital vein by injection of 0.5 ml of 1% Xylocaine, and a 20 gauge Teflon® catheter was inserted into the corresponding vein. This was connected with a three-way stopcock, 20 inch venotube, and a 20 ml syringe filled with normal saline. The patients were then placed on the bicycle ergometer in the erect position and imaged in the anterior projection with a Baird Atomic System Seventy-Seven multicrystal gamma camera.® Exercise studies preceded rest studies in all patients and subjects. Prior to exercise, the baseline heart rate and blood pressure were recorded. The electrocardiogram was monitored via telemetry throughout the exercise and recovery periods. Blood pressures were recorded by sphygmomanometer at one minute intervals during

TABLE 2. *Hemodynamic Response to Exercise in*

Patients	Sex	Age Years	BSA (m^2)	Heart Rate (beats/min) Rest	Heart Rate (beats/min) Exercise	Mean Blood Pressure (mm/Hg) Rest	Mean Blood Pressure (mm/Hg) Exercise	C.O. (L/min) Rest	C.O. (L/min) Exercise	C.I. ($L/min/m^2$) Rest	C.I. ($L/min/m^2$) Exercise	Ejection Fraction Rest	Ejection Fraction Exercise	EDV (ml) Rest	EDV (ml) Exercise	EDV (ml/m^2) Rest	EDV (ml/m^2) Exercise	SV (ml) Rest	SV (ml) Exercise
1	F	39	1.64	78	112	90	107	4.7	9.1	2.8	5.5	.66	.69	91	117	55	71	60	81
2	F	51	1.76	94	140	98	117	5.3	15.3	3.0	8.7	.80	.68	70	161	40	91	56	109
3	F	49	1.46	100	130	96	126	6.7	9.7	4.6	6.6	.70	.71	95	105	65	72	67	75
4	F	37	1.71	100	188	79	132	6.0	8.3	3.5	4.9	.86	.72	70	83	37	49	60	60
5	M	44	1.83	78	138	78	131	3.9	9.8	2.1	5.4	.58	.58	86	123	47	67	50	71
6	M	48	1.95	95	150	85	122	7.6	18.6	3.9	9.5	.80	.79	94	167	48	86	80	124
7	M	34	1.84	118	172	78	115	6.6	18.7	3.6	10.2	.54	.71	104	154	57	84	56	109
8	F	61	1.54	90	140	119	133	4.6	7.3	3.0	4.7	.70	.60	73	86	47	56	51	52
9	M	38	1.95	63	100	99	106	4.4	10.3	2.3	5.3	.57	.61	123	168	63	86	70	103
10	M	69	1.94	58	88	99	107	4.8	8.9	2.5	4.6	.66	.66	125	155	64	80	83	102

DMI diaphragmatic myocardial infarction, AMI anterior wall myocardial infarction, N no previous infarction, * positive stress treadmill test, (−)A negative adequate, (−)I negative inadequate, NYHA New York Heart Association functional classification, O normal wall motion, + abnormal wall motion (dyskinesia), NC no change.

exercise and every two minutes during the recovery period. Normal subjects were exercised to 85% of the maximal predicted heart rate for their age. In patients with known coronary artery disease as determined by cardiac catheterization or suspected coronary artery disease on the basis of a positive stress treadmill test, end points in exercise were defined as the onset of typical angina associated with a ≥1 mv depression of the S-T segment as recorded by electrocardiogram, life-threatening dysrhythmias, hypotension, muscle fatigue, or attainment of target heart rate. When any one of these events occurred, a bolus of 15 mCi technetium-99m pertechnetate was immediately injected, and counts were recorded at 50 msec intervals for one minute. Patients and subjects were then allowed to recover in the supine position until the EKG, heart rate, and blood pressure returned to baseline values. Prior to the injection of the second bolus of 15 mCi technetium-99m pertechnetate, a one minute background count over the precordium was obtained with the subject erect. The resting study was then performed at counting intervals of 50 msec.

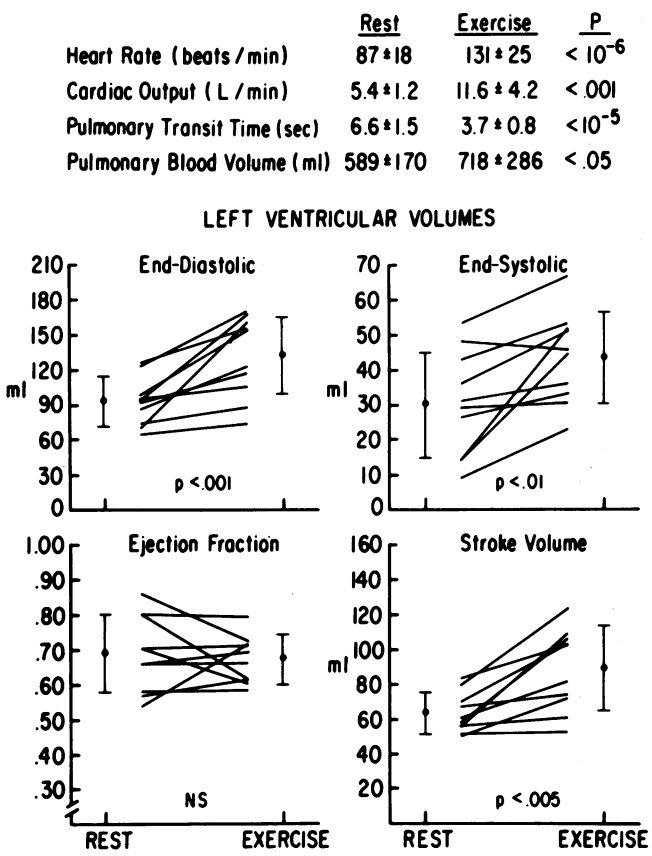


FIG. 2. Response to exercise in 10 patients with single vessel coronary artery disease (Mean age 47 years). During exercise mean ejection fraction decreases slightly while end-systolic volume, end-diastolic volume, and stroke volume all increase; NS = not significant.

Instrumentation and Data Processing

The Baird Atomic System Seventy-Seven computerized multicrystal gamma camera® was used for all dynamic studies. This instrument permitted counting rates greater than 400,000 counts per second, and counting intervals as brief as 50 msec. After initial computer correction of the data, the next step in data processing was to relate observed counts to discrete cardiac regions. A method has been developed to define borders of cardiac chambers, which depends upon a description of the time function of counts observed in many small regions over the precordium.[17] Individual cardiac chamber delay with bolus transit of tracer reflected by the time description permits accurate delineation of cardiac chamber boundaries. A degree of anatomic overlap occurs in some of the adja-

Patients with One Vessel Coronary Artery Disease

SV (ml/m²)		ESV (ml)		ESV (ml/m²)		PTT (sec)		PBV (ml)		PBV (ml/m²)					Radionuclide Wall Motion	
Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Myocard. Infarction	Bruce Treadmill Stress Test	NYHA Class.	Rest	Exercise
37	49	31	36	19	22	5.8	2.5	450	377	275	230	N	*	IV	0	NC
32	62	14	52	8	30	7.6	4.1	671	1046	381	594	N	*	IV	0	+
46	51	29	30	20	21	5.3	3.0	589	483	404	331	N	−(A)	IV	0	NC
35	35	10	23	6	13	5.9	4.0	590	552	345	323	N	−(I)	IV	0	+
27	39	36	51	20	28	6.6	3.8	430	621	235	339	N	*	IV	0	NC
41	64	14	44	7	23	5.8	3.2	735	991	360	508	N	−(I)	IV	0	+
30	59	48	45	26	24	7.9	3.8	871	1187	473	645	AMI	−(A)	I	+	NC
33	34	26	33	17	21	4.1	3.1	314	377	204	245	N	*	III	0	+
36	53	53	66	27	34	7.3	4.4	539	754	276	387	DMI	−(I)	IV	0	NC
43	53	43	53	22	27	9.4	5.3	751	794	387	409	N	*	IV	0	NC

cent cardiac chambers in any projection, and complex curves with several individual components are recorded over these adjacent cardiac regions. A computer technique has been developed using the first derivative of data to separate complex curves into individual components and to characterize each individual curve by the total counts and by mean transit time. The accurate delineation of anatomic regions which results is particularly important for the calculation of the ejection fraction.

Time activity curves from individual cardiac chambers may be used to calculate cardiac output, mean chamber volumes, and mean chamber transit time. A comparison of the systolic and diastolic counts within the left ventricle permits calculation of the ejection fraction. Observations in 33 patients demonstrated a correlation coefficient of 0.89 between this radionuclide technique and standard contrast biplane ventriculography. Ventricular volume changes during a single cardiac contraction were obtained by adding data from several cardiac contractions recorded at the time when tracer was maximal within the chamber. Phasic relationships to the cardiac cycle are retained, and the resulting curve which reflects count changes during the average cardiac cycle is related to changes in chamber volume by subtraction of background counts. Background counts are obtained by summing data from the initial transit of tracer just before and just after the time of maximal activity within the specific chamber. In addition to the quantitative data described, images are obtained of the initial tracer transit to permit appreciation of blood flow patterns. Supraimposition of 50 msec images from several cardiac cycles which retain phasic relationships throughout systole and diastole provide high count rate images reflecting chamber motion during a typical cycle. The images, which can be visualized in a dynamic cine format or static mode, permit assessment of wall motion abnormalities. Images are complementary with the quantitative data, and the greatest hemodynamic information results from a combined expression of the data in these two forms.

Validity of Volumetric Analysis

A new technique has been developed in this laboratory for obtaining cardiac output from the initial passage of tracer through the left ventricle in the anterior projection. This method employs standard angiographic planimetry of the static left ventricular end-diastolic volume image. End-diastolic volume is obtained by using the length-area measurement implied by the prolated ellipsoid model of revolution described by Dodge and associates.[7] A regression equation from 33 patients studied prior to catheterization gave the appropriate corrected end-diastolic volume. The correlation coefficient was 0.89. Stroke volume equals the product of end-diastolic volume and ejection fraction. The difference between stroke volume and end-diastolic volume provides the end-systolic volume. This volumetric technique using the first transit of radionuclide bolus was further verified in 33 normal subjects at rest and immediately following exercise with simultaneous determination of cardiac output using indocyanine green dye. Stroke volume determined from the computer generated ejection fraction and planimetered end-diastolic volume image revealed a correlation coefficient of 0.87. The corresponding cardiac outputs determined by both methods showed a correlation coefficient of 0.95.

The following list summarizes mathematical techniques for determination of left ventricular function

TABLE 3. *Hemodynamic Values in Patients with*

Patients	Sex	Age Years	Body Surface Area BSA (m^2)	Heart Rate (beats/min)		Mean Blood Pressure (mm/Hg)		Cardiac Output C.O. (L/min)		Cardiac Index C.I. (L/min/m^2)		Ejection Fraction		End Diastolic Volume EDV (ml)		End Diastolic Volume Index EDV (ml/m^2)		Stroke Volume SV (ml)	
				Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
1	M	67	1.91	70	120	76	106	4.6	10.3	2.4	5.4	.57	.27	116	317	61	166	66	86
2	M	48	1.85	68	82	79	97	5.2	7.8	2.8	4.2	.77	.75	100	127	54	69	77	96
3	M	58	1.96	77	120	81	67	7.5	6.2	3.8	3.2	.53	.31	185	167	94	85	98	52
4	M	42	1.88	105	156	89	127	6.4	10.1	3.4	5.4	.35	.33	173	196	92	104	61	65
5	M	59	1.81	65	110	103	115	4.6	15.3	2.5	8.5	.69	.52	103	267	57	146	71	139
6	M	46	1.91	96	120	106	116	6.5	9.2	3.4	4.8	.34	.31	200	247	105	129	68	77
7	M	64	1.88	68	108	77	104	4.5	9.2	2.4	4.9	.76	.48	87	178	46	95	66	85
8	F	60	1.51	80	120	94	150	5.9	8.6	3.9	5.7	.76	.55	97	131	64	87	74	72
9	M	59	1.80	60	88	83	113	3.8	9.5	2.1	5.3	.69	.56	93	187	52	104	64	108
10	M	50	1.97	70	100	113	147	5.6	15.6	2.8	7.9	.60	.52	123	264	62	134	80	156
11	M	38	2.21	70	130	84	121	7.1	9.9	3.2	4.5	.43	.28	238	271	108	123	102	76
12	M	60	1.85	60	144	99	122	7.0	17.4	3.8	9.4	.68	.52	171	232	92	125	115	121
13	M	42	2.21	90	156	92	156	5.2	19.7	2.4	8.6	.58	.46	100	274	45	124	58	126
14	M	56	1.85	95	112	98	130	5.6	10.4	3.1	5.6	.70	.43	85	216	46	117	59	93
15	M	41	1.95	55	78	93	113	4.1	6.8	2.1	3.5	.71	.64	106	147	54	75	75	94
16	M	40	2.32	86	152	87	127	9.6	17.0	4.1	7.4	.36	.32	309	349	133	150	111	112
17	M	49	1.96	95	150	95	112	7.1	13.7	3.6	6.9	.76	.69	93	132	47	67	71	91
18	M	57	1.93	54	150	108	127	4.9	16.8	2.5	8.7	.46	.39	196	287	102	149	90	112
19	M	60	1.91	70	84	119	134	3.7	3.9	2.0	2.0	.59	.30	91	143	48	81	53	46
20	M	59	1.91	70	90	93	101	4.5	9.4	2.4	4.9	.70	.62	92	168	48	88	64	104

DMI Diaphragmatic myocardial infarction, AMI Anterior myocardial infarction, N No previous infarction, (L.M.) Left main coronary stenosis, * Positive stress treadmill test, (−)I Negative inadequate, NYHA New York Heart Association functional classification, O Normal wall motion, + Abnormal wall motion (dyskinesia), ++ New area of abnormal wall motion (dyskinesia).

	Rest	Exercise	P
Heart Rate (beats/min)	75±15	119±26	$<10^{-5}$
Cardiac Output (L/min)	5.7±1.5	11.3±4.3	$<10^{-5}$
Pulmonary Transit Time (sec)	7.7±1.8	5.4±1.7	$<10^{-5}$
Pulmonary Blood Volume (ml)	727±269	953±367	<.02

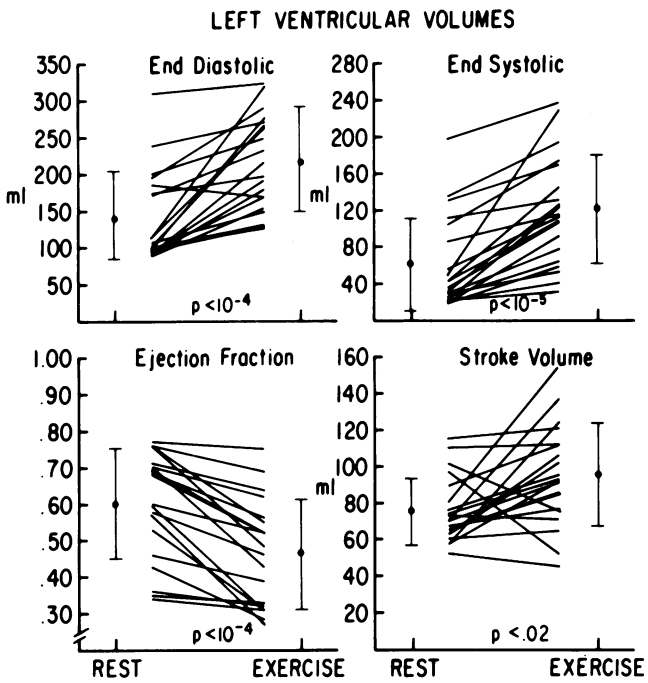


FIG. 3. Effects of exercise in 20 patients with more than one vessel coronary artery disease (Mean age 53 years). Note that during exercise there are significant increases seen in end-diastolic volume and end-systolic volume while ejection fraction is depressed.

from data obtained by the first passage of tracer through the central circulation.

1. ejection fraction (EF) percent

$$= \frac{\text{EDV counts} - \text{ESV counts}}{\text{EDV counts}} \times 100\%$$

2. left ventricular end-diastolic volume (LVEDV)

$$= \frac{0.85\ A^2}{l}$$

The radionuclide end-diastolic image was used to obtain the area (A) by planimetry and the length (l) by direct measurement.

3. stroke volume = LVEDV × EF
4. end-systolic volume = LVEDV − SV
5. cardiac output = SV × HR

Mean blood pressures recorded simultaneously with the rest and exercise study were used to calculate the mean systemic arterial pressure by the sum of one third the pulse pressure and end-diastolic pressure.[10]

The pulmonary mean transit time in seconds was obtained by the difference in the mean transit times

More Than One Vessel Coronary Artery Disease

Stroke Volume Index SV (ml/m²)		End Systolic Volume ESV (ml)		End Systolic Volume Index ESV (ml/m²)		Pulmonary Transit Time PTT (sec)		Pulmonary Blood Volume PBV (ml)		Pulmonary Blood Volume Index PBV (ml/m²)		Bruce Treadmill Stress Test			Radionuclide Wall Motion	
Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise	Myocard. Infarction	Treadmill Stress Test	NYHA Class	Rest	Exercise
35	45	50	231	26	121	9.6	6.7	766	948	401	496	N(L.M.)	*	III	0	+
42	52	23	32	12	17	6.7	3.3	581	431	314	233	DMI	*	IV	0	+
50	27	87	115	44	59	8.4	3.7	1055	383	538	196	DMI(L.M.)	*	III	+	++
32	35	112	131	60	70	5.6	4.9	598	825	318	439	AMI	*	IV	+	++
39	77	32	128	18	71	6.5	6.8	498	1734	275	958	DMI(L.M.)	*	II	0	+
36	40	132	171	69	90	8.0	5.1	869	781	455	409	DMI	*	III	+	++
35	45	21	93	11	49	9.1	6.8	683	1042	363	554	N	*	IV	0	+
49	48	23	59	15	39	6.2	5.1	610	731	404	484	N	*	IV	0	+
36	60	29	79	16	44	8.6	7.5	549	1188	305	660	N	*	IV	0	+
41	79	43	108	22	55	5.9	4.0	551	1040	271	512	DMI	*	III	+	++
46	34	136	195	62	88	13.5	8.5	1598	1403	723	635	AMI,DMI(L.M.)	−(I)	III	+	++
63	65	55	111	30	60	7.2	4.0	836	1162	452	628	N	*	II	0	+
26	57	42	148	19	67	7.3	2.6	630	850	280	373	N	*	II	0	+
32	63	25	123	14	66	7.2	4.9	678	848	366	458	N	*	III	0	+
38	48	31	53	16	27	7.1	5.2	485	586	249	300	DMI	*	III	0	+
48	48	198	237	85	102	7.1	5.9	1133	1672	488	721	DMI	−(I)	I	+	++
36	46	22	41	11	21	5.0	3.6	588	819	302	418	AMI	*	IV	0	+
47	58	106	175	55	91	8.1	4.4	658	1233	341	634	DMI	*	II	+	++
28	24	38	108	20	57	9.3	8.7	579	564	303	295	N(L.M.)	*	IV	0	+
34	54	28	64	15	34	7.8	5.2	585	812	306	495	N	*	III	0	+

of the left atrial and pulmonary artery radionuclide curves. The mean transit time is directly related to volume and inversely proportional to flow. Therefore, the pulmonary blood volume (in ml) is calculated by multiplying the cardiac output (in ml/sec) by the pulmonary mean transit time (in sec). The mean pulmonary transit time in normal subjects was 6.5 seconds. The corresponding pulmonary blood volume was 650 ml, which is approximately 11% of the cardiac output.

Measurements and Statistical Analyses

The paired student t-test was used to compare differences in individual rest and exercise measurements in each group. Significance of difference between groups was obtained by the comparison of means (unpaired t-test). Significance of data was determined at the level of $p < 0.05$.

Results

For purposes of analysis, the 60 subjects were divided into three groups. There were 30 normal controls (Group I), ten patients with documented one vessel coronary artery disease (Group II), and 20 patients with documented coronary artery disease involving more than one vessel (Group III). Within Group II, two patients were known to have sustained myocardial infarction prior to study. In Group III, 11 patients had sustained infarction prior to study.

The hemodynamic data for control subjects at rest and exercise are depicted in Table I and Figure 1. The electrocardiogram was normal at rest and no abnormalities were noted during exercise. Increased wall motion was noted in all normal subjects from rest to exercise. Although biological variation occurred among individual members within the group, a statistically significant change occurred in all left ventricular function measurements. For example, mean heart rate increased by 110% from rest to exercise ($p < 10^{-9}$). The corresponding increase in cardiac output was 192% ($p < 10^{-9}$). The mean increase in ejection fraction was 0.66 at rest to 0.80 at exercise ($p < 10^{-9}$). Stroke volume also showed a significant increase from 76 ± 20 ml to 102 ± 30 ml ($p < 10^{-8}$). On the other hand, the increase in end-diastolic volume was modest, with the mean value at rest being 116 ± 31 ml rising to 128 ± 31 ml at exercise ($p < 0.02$). End-systolic volume decreased from 40 ± 15 ml to 26 ± 9 ml ($p < 10^{-5}$). Pulmonary transit time also decreased significantly ($p < 10^{-9}$). However, pulmonary blood volume showed a mean increase from 640 ± 151 ml to 776 ± 264 ml ($p < 0.01$). Mean blood pressure increased in all normal subjects ($p < 10^{-6}$).

The hemodynamic data for each patient studied in

TABLE 4. *Mean Hemodynamic Changes In Three Study Groups*

	Mean		Standard Deviation		Standard Error		Paired *t*-Statistics	Mean % Change from Rest to Exercise
	Rest	Exercise	Rest	Exercise	Rest	Exercise		
Normal Subjects, Mean Age—34 years, Mean Body Surface Area—1.85 m²								
Heart Rate (beats/min)	81	170	±13	±21	3.21	3.75	$<10^{-9}$	↑110
Mean Blood Pressure (mm/Hg)	91	113	±15	±13	2.69	2.40	$<10^{-6}$	↑ 24
C.O. L/min	6.0	17.5	±1.3	±6.0	0.24	1.09	$<10^{-9}$	↑192
C.I. L/min/m²	3.3	9.4	±0.7	±2.9	0.13	0.52	$<10^{-9}$	↑185
Ejection Fraction	0.66	0.80	±0.06	±0.07	0.01	0.01	$<10^{-9}$	↑ 21
EDV (ml)	116	128	±31	±31	5.60	5.72	<0.02	↑ 10
EDV (ml/m²)	63	69	±16	±15	2.94	2.73	<0.03	↑ 10
SV (ml)	76	102	±20	±30	3.68	5.40	$<10^{-8}$	↑ 34
SV (ml/m²)	41	55	±10	±13	1.78	2.43	$<10^{-8}$	↑ 34
ESV (ml)	40	26	±15	±9	2.65	1.57	$<10^{-5}$	↓ 35
ESV (ml/m²)	22	14	±8	±6	1.52	1.02	$<10^{-5}$	↓ 36
PTT (sec)	6.5	2.8	+1.2	±0.7	0.21	0.13	$<10^{-6}$	↓ 57
PBV (ml)	644	776	±152	±264	28.19	49.07	<0.01	↑ 20
PBV (ml/m²)	345	416	±76	±130	14.05	24.14	<0.01	↑ 21
Patients with One Vessel Coronary Artery Disease, Mean Age—47 years, Mean Body Surface Area—1.76 m²								
Heart Rate (beats/min)	87	131	±13	±25	5.80	7.80	$<10^{-6}$	↑ 51
Mean Blood Pressure (mm/Hg)	92	120	±13	±11	4.07	3.40	<0.0007	↑ 30
C.O. L/min	5.4	11.6	±1.2	±4.3	0.38	1.4	<0.001	↑115
C.I. L/min/m²	3.1	6.5	±0.8	±2.1	0.24	0.67	<0.001	↑110
Ejection Fraction	0.69	0.67	±0.11	±0.07	0.03	0.02	NS	↓ 3
EDV (ml)	93	132	±20	±33	6.29	10.50	<0.001	↑ 42
EDV (ml/m²)	52	74	±10	±15	3.17	4.38	<0.01	↑ 42
SV (ml)	63	89	±12	±24	3.71	7.61	<0.005	↑ 39
SV (ml/m²)	36	50	±6	±11	1.88	3.40	<0.005	↑ 39
ESV (ml)	30	43	±15	±13	4.75	4.80	<0.01	↑ 43
ESV (ml/m²)	17	24	±8	±6	2.43	1.84	<0.02	↑ 41
PTT (sec)	6.6	3.8	±1.5	±0.8	0.48	0.26	$<10^{-5}$	↓ 42
PBV (ml)	594	718	±169	±286	53.36	90.30	<0.05	↑ 21
PBV (ml/m²)	334	401	±84	±140	26.58	44.33	NS	↑ 20
Patients with More than One Vessel Coronary Artery Disease, Mean Age—53 years, Mean Body Surface Area—1.93 m²								
Heart Rate (beats/min)	75	119	±15	±26	3.30	5.89	$<10^{-5}$	↑ 59
Mean Blood Pressure (mm/Hg)	93	118	±12	±19	2.69	4.18	$<10^{-5}$	↑ 27
C.O. L/min	5.7	11.3	±1.5	±4.3	0.33	0.96	$<10^{-5}$	↑ 98
C.I. L/min/m²	2.9	5.8	±0.7	±2.0	0.15	0.45	$<10^{-5}$	↑100
Ejection Fraction	0.60	0.46	±0.15	±0.15	0.03	0.03	$<10^{-4}$	↓ 23
EDV (ml)	138	216	±62	±66	13.79	14.84	$<10^{-4}$	↑ 57
EDV (ml/m²)	71	111	±27	±30	6.00	6.62	$<10^{-4}$	↑ 56
SV (ml)	76	96	±18	±28	4.03	6.22	<0.02	↑ 21
SV (ml/m²)	40	50	±9	±15	1.97	3.27	<0.01	↑ 25
ESV (ml)	62	120	±50	±59	11.15	13.22	$<10^{-5}$	↑ 94
ESV (ml/m²)	31	61	±23	±28	5.09	6.15	$<10^{-5}$	↑ 97
PTT (sec)	7.7	5.4	±1.8	±1.7	0.41	0.38	$<10^{-5}$	↑ 30
PBV (ml)	727	953	±269	±367	60.04	82.08	<0.02	↑ 31
PBV (ml/m²)	373	491	±114	±182	25.57	40.61	<0.02	↑ 32

Significance <0.05, NS Not statistically significant, ↑ Increase, ↓ Decrease.

Group II are shown in Table 2 and Figure 2. Eight of the ten patients were functional NYHA Class IV. Prior Bruce protocol stress treadmill tests were interpreted to show ischemic heart disease in five of the ten patients. In the remaining five patients, three had negative inadequate stress tests and two had negative adequate tests.

Radionuclide images of left ventricular contraction permitted assessment of wall motion at rest and exercise. The single patient (No. 7) in Group II, who had a wall motion abnormality at rest, had sustained a prior myocardial infarction and the abnormality did not change during exercise. Four patients with normal wall motion at rest developed segmental hypokinesia during exercise. In the remaining five patients with normal wall motion at rest, no discrete wall motion abnormality appeared during exercise. However, these patients failed to show the normal increase in wall motion during exercise, and the mean ejection fraction of .69 at rest showed an insignificant change to a mean of .67 during exercise. The mean end-diastolic volume increased from 93 ± 20 ml to 132 ± 33 ml ($p < 0.01$) during exercise. Whereas the mean end-systolic volume in normal subjects decreased with exercise, the

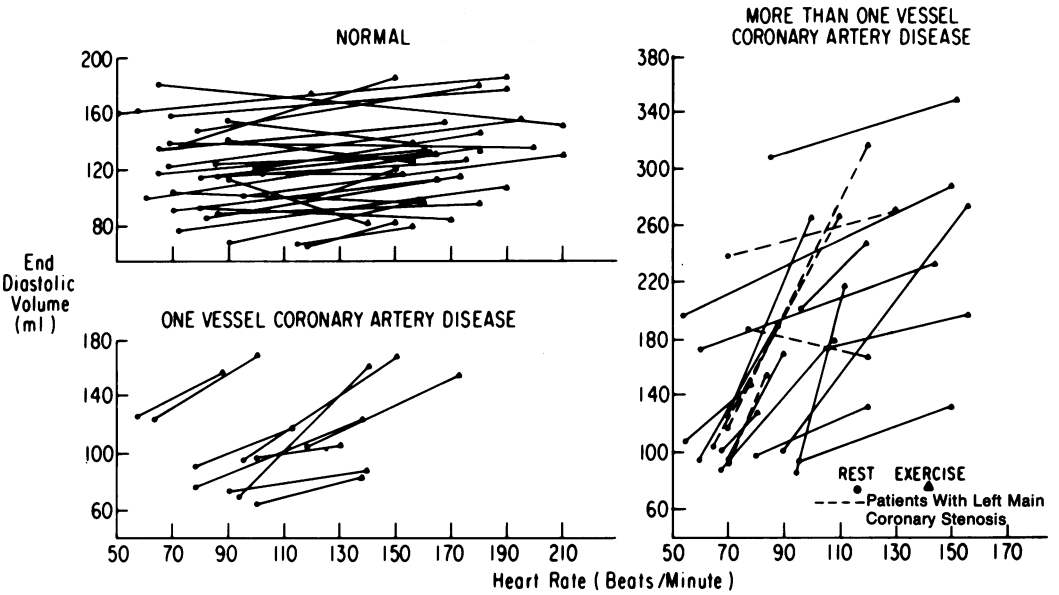


FIG. 4. Effects of increased heart rate upon left ventricular end-diastolic volume. The normal response reveals a slight variation; however, in patients with coronary artery disease and particularly patients with left main stenosis (except Patient 3, Group III), an increase in end-diastolic volume is observed.

mean end-systolic volume in patients in Group II increased from 30 ± 15 ml at rest to 43 ± 13 ml during exercise ($p < 0.01$).

The hemodynamic data for each patient in Group III are shown in Table 3 and Figure 3. Eleven of the 20 patients suffered prior myocardial infarction, and 18 had positive treadmill tests. Five patients had significant left main coronary artery stenosis. Seven patients exhibited abnormal wall motion at rest. However, all patients within the group exhibited a new area of segmental or global wall motion abnormality during exercise. All hemodynamic parameters changed significantly with exercise in this group. However, the most important changes occurred in end-diastolic volume, ejection fraction, and end-systolic volume. End-diastolic volume increased significantly ($p < 10^{-4}$) from 138 ± 62 ml at rest to 216 ± 66 ml at exercise. A corresponding increase was shown in end-systolic volume

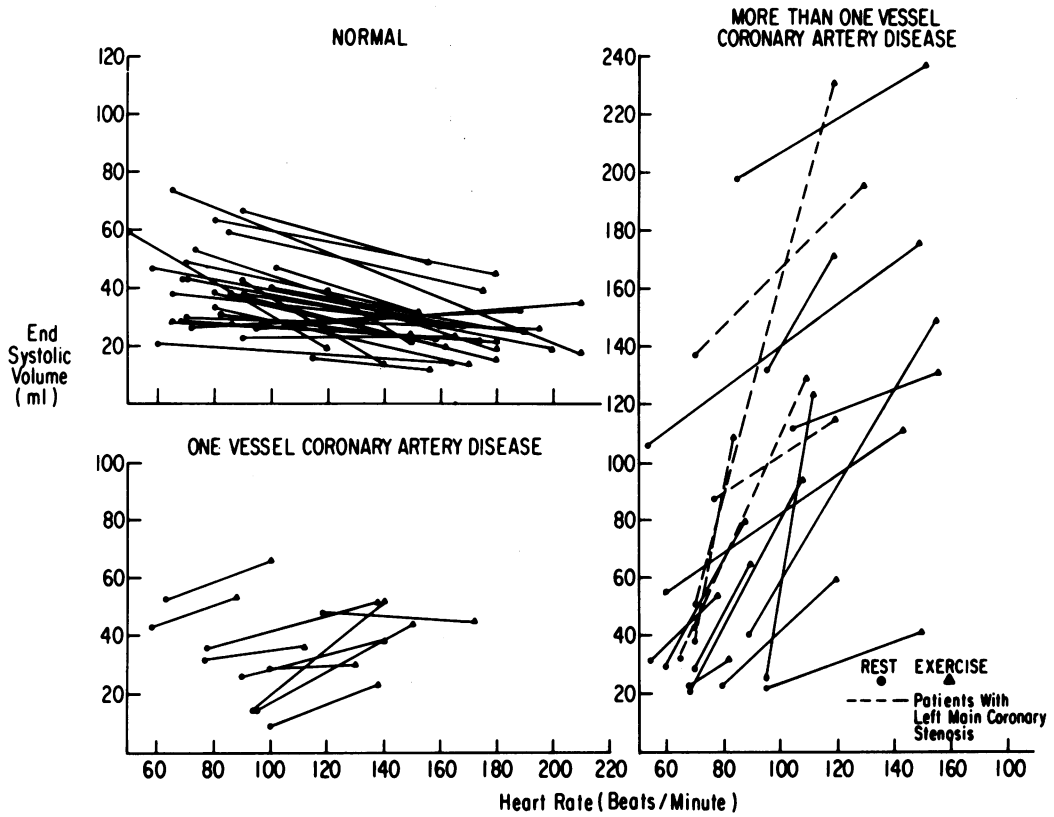


FIG. 5. Relationship between end-systolic volume and increases in heart rate. There is a decrease in end-systolic volume in the normal (except subject 7); however, in patients with one vessel (except Patient 7, Group II) and more than one vessel coronary artery disease, particularly left main stenosis, an increase in end-systolic volume is observed.

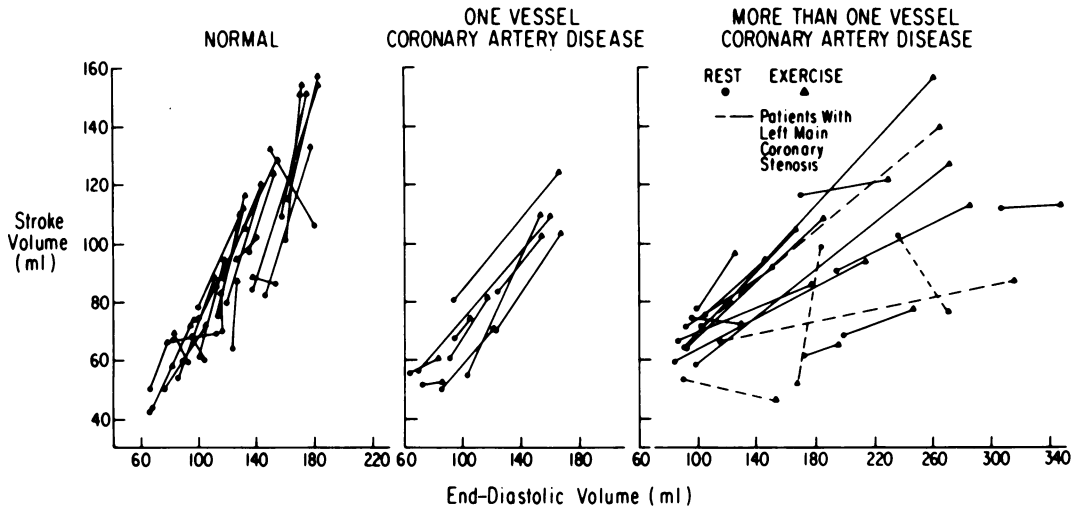


FIG. 6. Comparison of left ventricular function by plotting end-diastolic volume (initial diastolic fiber length) against stroke volume. The normal response demonstrates comparatively small increases in end-diastolic volume and results in a much greater increase in stroke volume. However, variation is observed in subjects 1, 4, 13, 18, 21, 27–30 in Group I. In patients with one vessel and more than one vessel coronary artery disease, a larger end-diastolic volume is needed to maintain stroke volume. In patients 8, 11, and 19 (Group III), an increase in end-diastolic volume results in a decrease in stroke volume. This suggests a descending limb to the Frank-Starling ventricular function curve.

from 62 ± 50 ml to 120 ± 50 ml ($p < 10^{-5}$). Moreover, the ejection fraction revealed a dramatic mean decrease of 0.60 at rest to 0.46 at exercise ($p < 10^{-4}$). A comparative summary of all measured hemodynamic parameters is presented in Table 4.

Changes in end-diastolic volumes with exercise occurred at different heart rates in Groups I–III (Fig. 4). Although the normal controls (Group I) show a statistically significant increase ($p < 0.02$) in end-diastolic volume, this occurred at a very high heart rate. However, in Groups II and III, a much greater increase in end-diastolic volume is observed ($p < .001$ in Group II and $p < 10^{-5}$ in Group III) at lower heart rates. Patients with left main stenosis demonstrate the most marked increments in end-diastolic volume with only a small change in heart rate from rest to exercise. The only exception to this observtion was Patient 3 in Group III, in whom end-diastolic volume fell with

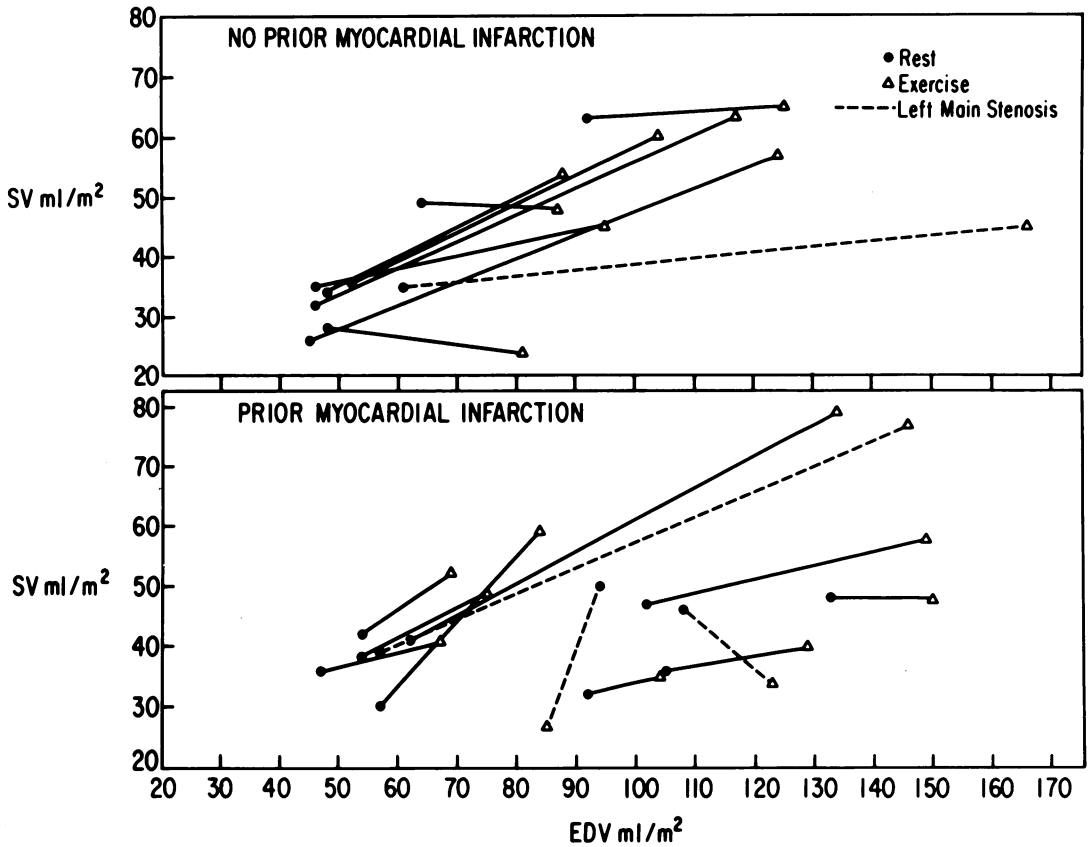


FIG. 7. End-diastolic volume index is compared to the stroke volume index in patients with more than one vessel coronary artery disease with and without prior myocardial infarction. All patients within this group demonstrated new areas of wall motion abnormalities at exercise not apparent at rest. Therefore, an ischemic response to exercise may be evoked even in patients with prior myocardial infarction.

exercise. However, this patient also became hypotensive during the exercise (Table 3).

The magnitude of change in end-systolic volume with exercise also occurred at different heart rates in the three groups (Fig. 5). The controls (Group I) show a significant decrease ($p < 10^{-5}$), whereas Groups II and III reveal statistically significant increases ($p < .01$ and $p < 10^{-5}$) at lower heart rates.

Ventricular function curves compare the end-diastolic volume required to achieve the stroke volume at rest and exercise in the three groups (Fig. 6). Large increases in end-diastolic volume from rest to exercise are required to maintain the stroke volume in Group III, and patients in Group II showed less increase in stroke volume at any end-diastolic volume in comparison to Group I. Patients 8, 11, and 19 in Group III actually decreased stroke volume with an increase in end-diastolic volume, and two of these patients had left main coronary artery stenosis.

Left ventricular function curves for patients in Group III with and without prior myocardial infarction are shown in Figure 7. With the exception of Patients 11 and 16, all had evidence of myocardial ischemia on the basis of a positive stress treadmill test. Furthermore, all patients revealed new areas of segmental or global wall motion abnormality during exercise which were not present at rest during radionuclide studies. These data suggest that myocardial ischemia can be demonstrated even in patients with myocardial fibrosis resulting from a previous myocardial infarction.

Data processed images of end systole superimposed on the image of the cardiac border during diastole document wall motion in a normal subject (A), a patient with one vessel coronary disease (B), and a patient with more than one vessel involvement (C) (Fig. 8). Wall motion was normal in the control subject at rest and during exercise. In patients B and C, wall motion was normal at rest, but obvious abnormalities appeared during exercise. The left ventricular volume curves show essentially normal resting ejection fractions and end-diastolic volumes in all three patients (Fig. 9). However, during exercise, the normal subject increased left ventricular ejection fraction with no change in end-diastolic volume and a decrease in end-systolic volume. In the patient with one vessel disease, decreased ejection fraction during exercise was associated with a moderate increase in both end-diastolic and end-systolic volume. In the patient with stenosis of more than one coronary artery, a large decrease in the ejection fraction was accompanied by a very large increase in end-diastolic and end-systolic volumes.

A statistical analysis of left ventricular function in the three groups is shown in Table 5. Comparison between the normal ventricles (Group I) and the patients

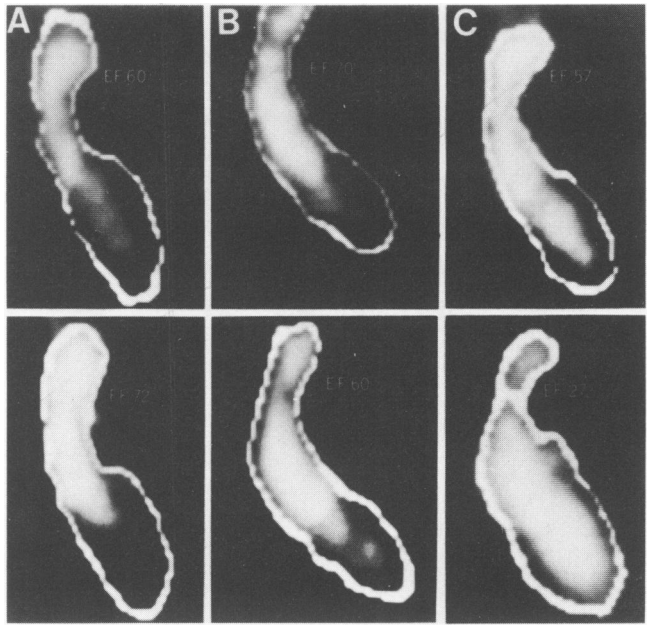


FIG. 8. These static left ventricular images were obtained at rest (top row) and exercise (bottom row) in a normal subject (A), patient with one vessel coronary artery disease (B), and a patient with left main and circumflex coronary artery stenosis (C). The outer border of each image represents the border of left ventricular end-diastolic outline and ascending aorta. Within this border is the residual end-systolic tracer.

with one vessel coronary disease (Group II) reveals a statistically significant lower heart rate ($p < 0.00002$), cardiac index ($p < 0.01$), and ejection fraction ($p < 0.00002$) in Group II during exercise. Moreover, the end-systolic volume index is larger at exercise in Group II ($p < 0.00002$). Left ventricular function at rest shows no significant differences between the two groups. Comparison between normal subjects (Group I) and patients with more than one vessel disease (Group III) at exercise reveals significantly lower heart rate, cardiac index, and ejection fraction in Group III. In addition, the end-diastolic volume index ($p < 10^{-8}$) and the end-systolic volume index ($p < 10^{-9}$) both were larger in Group III during exercise. At rest, the only significant difference between the groups was a larger end-diastolic volume index in Group III ($p < 0.05$). A comparison between patients with one vessel coronary disease and patients with more than one vessel stenosis reveals no difference in heart rate or cardiac index at rest and exercise. However, during exercise Group III has a lower ejection fraction ($p < 0.0002$) and a larger end-diastolic volume index ($p < 0.001$) and end-systolic volume index ($p < 0.0003$) than Group II. The only difference during rest was a larger end-diastolic volume index ($p < 0.05$) in Group III. The similar mean blood pressure in all groups suggests that left ventricular volume

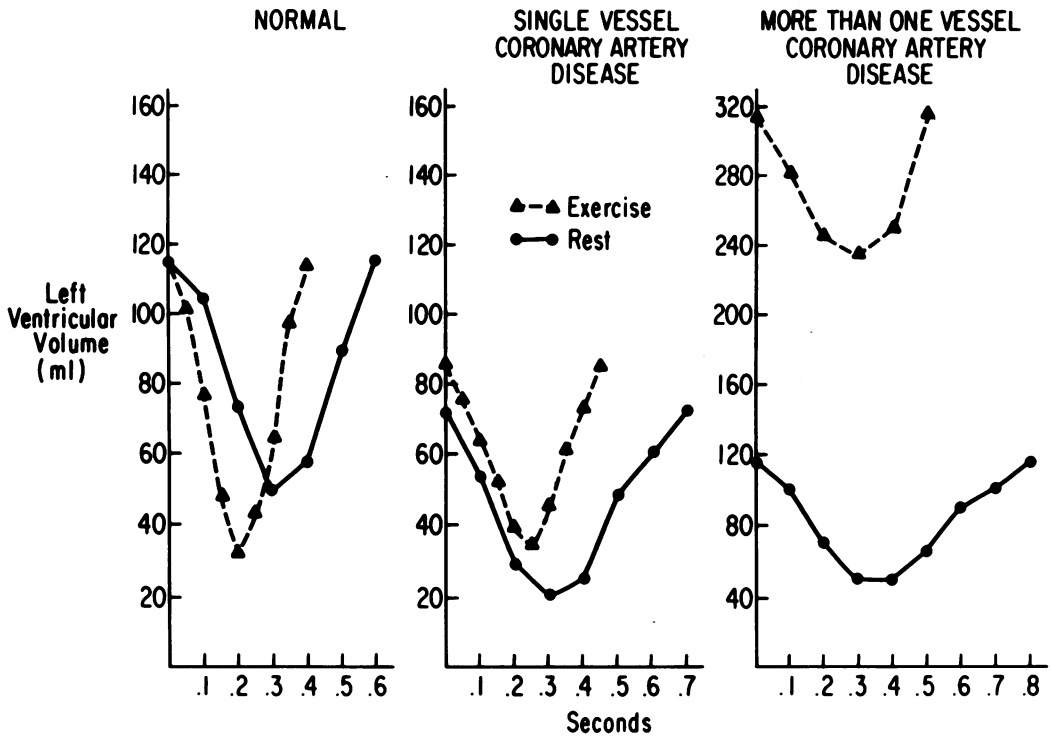


FIG. 9. Response to exercise. These left ventricular volume curves were obtained in the three patients illustrated in Figure 8. During exercise, end-diastolic volume is unchanged in the normal and end-systolic volume is decreased. In patients with one vessel and more than one vessel coronary artery disease, a progressive increase in end-diastolic and systolic volumes is observed.

changes are not caused solely by differences in left ventricular after-load in the three groups. The data describing left ventricular function during exercise clearly separate the three groups.

Discussion

In a study of the linear velocity of blood flow in 1927, Blumgart and Yens introduced the use of radioactive tracers in clinical cardiology.[2,3] In 1949, Prinzmetal and associates recorded passage of radioactivity through the heart using a Geiger counter and analyzed quantitative differences produced by circulatory abnormalities.[24] Use of a nondiffusible radioactive tracer by Shipley and colleagues permitted the determination of cardiac output without arterial sampling.[28] In 1957, Huff and coworkers used data obtained from four detectors over the chest to calculate central transit times and blood volume.[15] After these initial studies, widespread use of isotopes in clinical cardiology was predicted because of their innocuous nature. Inaccuracy, however, caused by difficulty in positioning detectors over a known cardiac region, limited routine application of these techniques. Refinement of instrumentation

TABLE 5. *Statistical Analysis Between Groups*

Hemodynamic Parameters	Normal Ventricle vs. One Vessel Coronary Artery Disease		Normal Ventricle vs. More Than One Vessel Coronary Artery Disease		One Vessel Coronary Artery Disease vs. More Than One Vessel Coronary Artery Disease	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Heart Rate (beats/min)	NS	↓<0.00002	NS	↓<10^{-9}	NS	NS
Mean Blood Pressure (mm/Hg)	NS	NS	NS	NS	NS	NS
Cardiac Index (L/min/m²)	NS	↓<0.01	NS	↓<0.00002	NS	NS
Ejection Fraction (%)	NS	↓<0.00002	NS	↓<10^{-9}	NS	↓<0.0002
Left Ventricular End-Diastolic Index (ml/m²)	NS	NS	NS	↑<10^{-8}	↑<0.05	↑<0.001
Left Ventricular Stroke Volume Index (ml/m²)	NS	NS	NS	NS	NS	NS
Left Ventricular End-Systolic Volume (ml/m²)	NS	↑<0.00002	↑<0.05	↑<10^{-9}	NS	↑<0.003
Pulmonary Blood Volume Index (ml/m²)	NS	NS	NS	NS	NS	NS

NS Not statistically significant, ↓ significant decrease, ↑ significant increase, statistical significance < 0.05.

for rapid imaging and quantitation of radioactivity over a large area has renewed interest in radionuclide angiocardiography. Initial studies with these camera-like detectors provided a sequential pictorial display of the intracardiac passage of radionuclides.[11,18,20] Other studies have quantitated regional changes in radioactivity over the heart.[23] The results of these and similar studies suggest a variety of useful clinical applications of these techniques, particularly in patients with coronary artery disease.

The experimental design of the present study consists of an initial passage of tracer through the central circulation, a method commonly called the *first-pass technique*. Although multigated studies using equilibration of technetium human serum albumin within the circulation have been the most popular method of evaluating left ventricular function at rest and during exercise,[4,31,34] it is felt that the first-pass technique provides a broader understanding of changes in chamber volume within the entire central circulation. In addition, since all previous noninvasive studies have been performed in the supine position, the technique of first-pass study has enabled the performance of measurements in the more natural erect position at rest and during exercise. In this study, exercise data were obtained prior to the resting study. This was done to alleviate the problem of subtracting background counts during exercise. Adequate recovery times from ten to 30 minutes were allowed in which heart rate, blood pressure, and electrocardiographic tracings returned to pre-exercise levels, assuring reliable left ventricular hemodynamic values at rest.

The effects of exercise upon the central circulation in normal erect human subjects have been studied by numerous investigators during the past two decades. Augmentation of cardiac output with exercise has been shown to result from a large increase in heart rate and a moderate increase in stroke volume.[1,6,8,12,13,21] Remarkable left ventricular hemodynamics can be achieved in well conditioned athletes. An extraordinary example of cardiac performance was observed in a college athlete at maximal exercise to exhaustion (Table 6). This study simply illustrates the extremes of left ventricular function at which man is able to perform.

Data obtained in the present studies in controls (Group I) revealed that augmentation of cardiac output from rest to exercise resulted primarily from a 110% increase in heart rate. Moreover, a 34% increase in stroke volume contributed to the increase in cardiac output during exercise. The stroke volume increased with exercise in the erect position more than the end-diastolic volume, which caused an increase in left ventricular ejection fraction. Therefore, the end-systolic volume decreased significantly from rest to exercise. The increase in cardiac output greatly decreased the pulmonary transit time, and the pulmonary blood volume increased with maximal exercise in the group of normal subjects, but large individual variation was observed.

TABLE 6. *Cardiac Performance in a 22-Year-Old Varsity Collegiate Swimmer*

	Rest	Exercise
Heart rate (beats/min)	51	210
Blood pressure (mm/Hg)	112/74	182/68
Ejection fraction (%)	74	97
End-diastolic volume (ml)	201	278
End-systolic volume (ml)	52	8
Stroke volume (ml)	149	270
Cardiac output (L/min)	7.6	56.6

A comparison of left ventricular hemodynamic parameters measured in a world-class college athlete after six months of intensive training. These data suggest that cardiac output at maximal exercise results from an extreme increase in heart rate associated with a large increase in end-diastolic volume. Moreover, augmentation of myocardial contractility (ejection fraction) is enhanced, which results in an 8 ml residual at end-systole. This study was taken from unpublished data determining the effects of intensive training upon the central circulation in 18 college athletes.

In the ten patients with documented single vessel coronary artery disease (Group II), two patients had prior myocardial infarction. Patient 7 had a negative adequate treadmill test, while Patient 9 had a negative inadequate test. In both patients, abnormal wall motion studies at catheterization were also documented at rest during the radionuclide study. Furthermore, during the course of the exercise study, no areas of abnormal wall motion were noted. A 115% increase in cardiac output occurred with a 51% increase in heart rate and a 39% increase in stroke volume. In this group, both the end-diastolic and end-systolic volume increased during exercise, resulting in no significant change in ejection fraction from rest to exercise. The failure to increase left ventricular ejection fraction and the increase in end-systolic volume with exercise provided clear separation between Groups I and II. Therefore it becomes apparent tha, in patients with one vessel disease, maintenance of cardiac output and stroke volume requires an increase in end-diastolic volume and heart rate. This demonstrates the early manifestation of cardiac dilatation (Frank-Starling relationship), which serves as a protective mechanism for preservation of cardiac output.

Wall motion appeared normal at rest in nine of ten patients in Group II evaluated by radionuclide scans. However, in four of ten patients, exercise-induced ischemia produced segmental wall abnormalities which were not apparent at rest. This observation has also been documentd by other investigators.[4,9,27] Further-

more, prior stress treadmill electrocardiograms in five of the ten patients were either negative inadequate, negative adequate, or in one patient uninterpretable secondary to pre-existing electrocardiographic changes. Although the numbers are small in this group, it appears that exercise radionuclide angiocardiography may be more sensitive in selecting those patients with ischemic myocardium compared to those who have had prior myocardial infarctions and no ischemia.

Patients in Group III attained a 98% increase in cardiac output by a 59% increase in heart rate and a 21% increase in stroke volume. However, the increase in stroke volume required a large increase in left ventricular volume. The end-diastolic volume increased 57% to an average of 216 ml, and the end-systolic volume increased 94% to an average of 120 ml. Although the stroke volume increased, the ejection fraction decreased from rest to exercise because of the increase in end-diastolic volume. Therefore, stroke volume is preserved by extremely large increases in end-diastolic volume with resultant acute cardiac dilatation. This emphasizes the importance of pre-load (Frank-Starling mechanism) as a basis for preservation of left ventricular function during exercise. Intercomparison among Groups I through III illustrates several important points (Table 5). Mean blood pressure was not statistically significant. Although this measurement was obtained peripherally, it implies that observed left ventricular dysfunction seen at exercise was not on the basis of increased after-load. As the extent of vessels involved with coronary artery disease increases, myocardial contractility decreases with exercise. Moreover, in order to maintain stroke volume and cardiac output, large increases in end-diastolic volume and end-systolic volume occur. A clear separation was observed among the three groups (Table 5), on the basis of ejection fraction, end-diastolic volume, and end-systolic volume.

Although pulmonary blood volume increased from rest to exercise in each group (Figs. 1–3), there was no statistical difference among the groups (Table 5). Consequently, it is felt that pulmonary blood volume analysis is of limited value as a predictor of ischemic coronary artery disease.

Braunwald and associates, as well as other investigators, have shown that increased cardiac output induced by exercise in normal man is a result of increased heart rate. This has been referred to as the "masking effect" of the Frank-Starling mechanism produced by exercise tachycardia. This effect is further supported by the fact that fixed atrial pacing during exercise in experimental animals and normal subjects demonstrates an increase in end-diastolic dimensions of the left ventricle.[8,14,19,29,30,32,33] The present data support those of previous investigators showing an increase in stroke volume from rest to exercise in erect man. Furthermore, the data also illustrate that there is a slight increase in end-diastolic volume in erect man at exercise. In patients with induced ischemic coronary artery disease during exercise, acute cardiac dilatation was observed. Sharma and associates also noted this dilatation in exercising patients with coronary artery disease with a greater increase in end-diastolic volume than stroke volume causing a decrease in ejection fraction.[27] The Frank-Starling mechanism is clearly important in the preservation of stroke volume in patients with ischemic coronary artery disease with an increase in cardiac output induced by exercise.

In summary, resting and exercise radionuclide angiocardiography affords a unique and thorough evaluation of left ventricular hemodynamic parameters in patients with coronary artery disease. These studies also demonstrate that the use of radionuclide angiocardiograms at rest and during exercise may prove a valuable adjunct to the screening of patients with chest pain. Moreover, the technique permits a meaningful prognosis to be made and it is also of value in establishing the diagnosis and in objective follow-up of patients with myocardial ischemia.

References

1. Bevegard, S., Holmgren, A. and Jonsson, B.: The Effect of Body Position on the Circulation at Rest and During Exercise, with Special Reference to the Influence on the Stroke Volume. Acta Physiol. Scand., 49:279, 1960.
2. Blumgart, H. L., and Yens, O. C.: Studies in the Velocity of Blood Flow. I. The Method Utilized. J. Clin. Invest., 4:11, 1927.
3. Blumgart, H. L. and Weiss, S.: Studies in the Velocity of Blood Flow. VII. The Pulmonary Circulation Time in Normal Resting Individuals. J. Clin. Invest., 4:399, 1927.
4. Borer, J. S., Bacharach, S. L., Green, M. V., et al.: Real-time Radionuclide Cineangiography in the Non-invasive Evaluation of Global and Regional Left Ventricular Function at Rest and During Exercise in Patients with Coronary Artery Disease. N. Engl. J. Med., 296:839, 1977.
5. Bruce, R. A.: Exercise Testing of Patients with Coronary Heart Disease. Ann. Clin. Res., 3:323, 1971.
6. Chapman, C. B., Fisher, J. N. and Sproule, B. J.: Behavior of Stroke Volume at Rest and During Exercise in Human Beings. J. Clin. Invest., 30:1208, 1960.
7. Dodge, H. T., Hay, R. E. and Sandler, H.: An Angiocardiographic Method for Directly Determining Left Ventricular Stroke Volume in Man. Circ. Res., 11:739, 1962.
8. Epstein, S. E., Robinson, B. F., Kahler, R. L. and Braunwald, E.: Effects of Beta-adrenergic Blockage on Cardiac Response to Maximal and Submaximal Exercise in Man. J. Clin. Invest., 44:1745, 1965.
9. Eubanks, D. R., Tsakiris, A. G., Davis, G. D., et al.: Left Ventricular Volumes During Exercise-induced Angina in Patients with Coronary Artery Disease. Circulation, 42(Suppl. 3:111, 1970.
10. Geddes, M. E.: The indirect measurement of blood pressure in man. *In* The Direct and Indirect Measurement of Blood Pressure. Chicago, Year Book Medical Publishers, Inc., 1970, p. 70.
11. Graham, T. P., Goodrich, J. K., Robinson, A. E., et al.: Scinti-

angiocardiography in Children. Rapid Sequence Visualization of the Heart and Great Vessels After Intravenous Injection of Radionuclide. Am. J. Cardiol., 25:387, 1970.
12. Guyton, A. C., Jones, C. E. and Coleman, T. G.: Cardiac output in muscular exercise. *In* Circulatory Physiology: Cardiac Output and its Regulation. Philadelphia, W. B. Saunders Co., 1973, p. 436.
13. Holmgren, A. and Ovenfors, C. O.: Heart Volume at Rest and During Muscular Work in the Supine and in the Sitting Position. Acta Med. Scand., 167:267, 1960.
14. Horwitz, L. D., Atkins, J. M. and Leshin, S. J.: Role of the Frank-Starling Mechanism in Exercise. Circ. Res., 31:868, 1972.
15. Huff, R. L., Parrish, D. and Crockett, W.: A Study of Circulatory Dynamics by Means of Crystal Radiation Detectors on the Anterior Thoracic Wall. Circ. Res., 5:395, 1957.
16. Jones, R. H., Goodrich, J. K. and Sabiston, D. C., Jr.: Quantitative Radionuclide Angiocardiography in Evaluation of Cardiac Function. Surg. Forum, 22:128, 1971.
17. Jones, R. H. and Scholz, P. M.: Data enhancement techniques for radionuclide cardiac studies. *In* Medical Radionuclide Imaging, vol. 2. Vienna, International Atomic Energy Agency, 1977.
18. Kriss, J. P., Enright, L. P., Hayden, W. G., et al.: Radioisotopic Angiocardiography. Wide Scope of Applicability in Diagnosis and Evaluation of Therapy in Disease of the Heart and Great Vessels. Circulation, 43:792, 1971.
19. Liljestrand, G., Lysholm, E. and Nylin, E.: Immediate Effects of Muscular Work in the Stroke and Heart Volume in Man. Scand. Arch. Physiol., 80:265, 1938.
20. Mason, D. T., Ashburn, W. L., Harbet, J. C., et al.: Rapid Sequential Visualization of the Heart and Great Vessels in Man Using the Wide-field Anger Scintillation Camera. Radioisotope-angiography Following Injection of Technetium-99m. Circulation, 59:19, 1969.
21. Mitchell, J. H., Sproule, B. J. and Chapman, C. B.: The Physiological Meaning of the Maximal Oxygen Intake Test. J. Clin. Invest., 37:538, 1958.
22. Peterson, K.: Improved Diagnosis of Coronary Artery Disease During Exercise Testing Using a Computer Processed Thallium-201 Image. Circulation, 54 (Suppl. 2):207, 1976.
23. Pierson, R. N., Jr., Kriss, J. P., Jones, R. H. and MacIntyre, W. J., eds.: Quantitative Nuclear Cardiography. New York, John Wiley and Sons, 1975.
24. Prinzmetal, M., Corday, E. Spritzler, R. H., et al.: Radiocardiography and its Clinical Applications. JAMA, 130:167, 1949.
25. Ritchie, J. L., et al.: Myocardial Imaging with Thallium-201 at Rest and During Exercise: Comparison with Coronary Arteriography and Resting and Stress Electrocardiography. Circulation, 56:66, 1977.
26. Rivas, F., Cobb, F. R., Bache, R. J. and Greenfield, J. C., Jr.: Relationship Between Blood Flow to Ischemic Regions and Extent of Myocardial Infarction. Circ. Res., 38:439, 1976.
27. Sharma, B., Goodwin, J. F., Raphael, M. J., et al.: Left Ventricular Angiography on Exercise: A New Method of Assessing Left Ventricular Function in Ischemic Heart Disease. Br. Heart J., 38:59, 1976.
28. Shipley, R. A., Clark, R. E., Leibowitz, D., et al.: Analyses of Radiocardiogram and Heart Failure. Circ. Res., 1:428, 1953.
29. Starling, E. H.: The Linacre Lecture on the Law of the Heart. Given at Cambridge, 1915. London, Longmans, 1918.
30. Starling, E. H.: On the Circulatory Changes Associated with Exercise. J. R. Army Med. Corps, 34:258, 1920.
31. Strauss, H. W., Zaret, B. L., Hurley, P. J., et al.: A Scintiphotographic Method for Measuring Left Ventricular Ejection Fraction in Man without Cardiac Catheterization. Am. J. Cardiol., 28:575, 1971.
32. Vatner, S. F. and Pagani, M.: Cardiovascular Adjustments to Exercise: Hemodynamics and Mechanisms. Prog. Cardiovasc. Dis., 19(2):91, 1976.
33. Vatner, S. F., Franklin, D., Higgins, C. B., et al.: Left Ventricular Response to Severe Exertion in Untethered Dogs. J. Clin. Invest., 51:3052, 1972.
34. Zaret, B. L., Strauss, H. W., Hurley, P. J., et al.: A Noninvasive Scintiphotographic Method for Detecting Regional Ventricular Dysfunction in Man. N. Engl. J. Med., 284:1165, 1971.
35. Zaret, B. L., Strauss, H. W., Martin, N. D., et al.: Non-invasive Assessment of Regional Myocardial Perfusion with Potassium 43 at Rest, Exercise, and During Angina Pectoris. Circulation, 46 (Suppl. 2):11, 1972.

Discussion

Dr. Frank C. Spencer (New York, New York): To those of you who are not familiar with the field, it should be emphasized that this probably represents the best data in the world on the measurement of cardiac function in the ambulatory patient by noninvasive techniques. It is typical of the kind of scholarly presentation we have come to expect from Duke. Similarly, it is a tribute to Dr. Sabiston's leadership in guiding young men into basic investigation that produces work of this quality.

The physiologic fact that in trained olympic swimmers, the cardiac output may momentarily exceed 50 liters is quite significant in itself. A widespread clinical application of the technique is that it may permit the noninvasive measurement of cardiac function before and after different types of cardiac operations.

A popular subject on both television and the newspapers is the influence of coronary bypass on longevity and whether the benefit is worth the cost. As President Scott has emphasized, this has been quickly seized upon by so-called "health planners" with their over-zealous efforts at regulation. A truism with any operation is that it should benefit function more than it harms. With coronary bypass, the question is whether the increase in blood flow to ischemic heart muscle outweights the possible harm from the operative procedure. What has been missing to date is a simple way of measuring cardiac function both before and after operation by a noninvasive technique, rather than our existing methods of the complex cardiac catheterization, which is both time consuming, expensive, and often not possible because the patient feels well and does not wish to undergo catheterization.

A screening test like this one has great potential. Note the remarkable study of ejection fraction with coronary disease, with the example of the ejection fraction decreasing from 0.74 to 0.26 with exercise. One can imagine the possible harm, or even death, that could result from a patient like this undertaking unsupervised jogging.

To emphasize the importance of the coronary bypass question even further, the fact that coronary disease is the leading cause of death in the Caucasian male throughout the world, including New Zealand, Australia, U.S.A., England, and Finland, is a crucial fact. A recent world-wide study has found the frequency of coronary disease in middle-aged U.S. males to be about 8%, certainly, an extremely common problem.

Our data at New York University with coronary bypass reported at the American Thoracic Association Meeting last April strongly indicate a great improvement in longevity in our experience with over 1100 patients in the past 7 years. These data, appearing in print soon, demonstrate a survival of 88% at 5 years, including the average operative mortality, and the survival curve is virtually identical to that of the normal population. With screening tests as shown in this publication, decisions can be reached much more quickly, rather than the time consuming method of evaluating the beneficial effects over a period of several years in randomized studies.

So, I closing, I would like to ask Drs. Jones and Sabiston two